

The immune system maintains integrity of an organism

Zlatko Dembic

Department of Oral Biology, Faculty of Dentistry, University of Oslo,

Sognsvannsveien 10, PO Box 1052 Blindern,

0316 Oslo, Norway

Abstract

The workings of the immune system, in philosophical terms, follow *integrity* principle, which I regard as a sum of homeostatic (integrity preservation) and analytic (integration) functions of tissues within an organism. It states that damage of particular tissue is followed by restitution of integrity by interplay of positive and negative feedback loops. Such principle is seen as a driving force for evolution of the immune system from primordial integrity-repair mechanism. The most common disruption of integrity in vertebrates is caused by microorganisms, which can initiate the immune response. Natural selection favored the host/commensal rather than host/pathogen relationship, and consequently tolerance towards commensals co-evolved with the initiation of the immune response against pathogens (including host tolerance). However, the necessity of developing commensal tolerance by the immune system dissociated (evolutionarily) its *analytic* part (the afferent arm; started by disruption of tissue integrity) from its *restorative* part (the efferent arm) in 'space' and 'time'. The renewal process includes bio-destruction of an intruder and restoration of integrity. The *analysis* - *renewal* separation in space and time further necessitated evolution of characteristics such as immune specificities, chemotaxis and multicellular crosstalk. Due to various selective pressures, the immune systems of vertebrates exhibit diverse communications between cells of the afferent and efferent arms of the immune response. Diversification of the immune repertoire, in turn, facilitated the establishment of long-term memory. These mechanisms work to protect commensals (potential symbionts), reject harmful pathogens and neglect the rest of microbiota. Therefore, the role of the immune system is to dynamically maintain the integrity of a being, in a common effort with other tissues and with a little help from our tiny friends (commensals).

Introduction

A simple explanation for all experimental and clinical observations is a hard task for any theory that aims to describe the workings of the immune system. The self-nonself (S/NS) discrimination principle describes in simple terms how an individual's repertoire of potential reactivities against pathogens is made of clonally distributed antigen receptor molecules on immunocytes (B and T lymphocytes). These could either bind to self- or nonself-epitopes. Bretscher and Cohn proposed a model of lymphocyte activation that involves a two-signal activation mechanism, which revolutionized our concept about the initiation of the immune response ¹. The concept was questioned with regard to a problem (among others) of generation of the first T helper (Th) effector cells ². Langman and Cohn, in Associative Antigen Recognition model (AAR) ^{3; 4}, proposed it be a germ-line encoded process. According to AAR, every naive T helper cell that is not eliminated by self antigens during the early period of embryonic life and given enough time would eventually become an effector cell, which in turn would facilitate activation of other cognate naïve Th cells. To explain this process other models involve co-stimulation of helper T cells via antigen-presenting cells (APCs). Janeway and Medzhitov in *Stranger (Pathogenicity)* ^{5; 6} or Matzinger in *Danger* ^{2; 7-9} models, assigned an alarming signal for the initiation of the immune response (and the generation of the first Th effectors) upon “intrusion of the pathogen” or when cellular (or tissue) death (necrosis), distress and disruption is sensed. These concepts are solely based on *space* discrimination principle (self/nonself; host/stranger and non-dangerous/dangerous), because the difference between *nonself*, *stranger* and *dangerous* might be purely semantic. There are other hypotheses like *Morphostasis* (tissue homeostasis), *Cytokine burst*, *Antigen localization*, and *Calibration* by Cunliffe, Weigle, Zinkernagel, and Sinclair and Anderson ¹⁰⁻¹⁴, which stressed the importance of the context of antigenic challenge. However, these left out the *time* component, which is a term that I would like to use as to describe a delay between afferent and efferent arms of the immune

response. The delay is a result of a putative *analytic* crosstalk involving tissues, immunocytes and cells of the innate immunity with outcomes such as the generation of memory, class, and feedback of immune responses, and the restoration of tissue integrity. Recent extension of the *Danger* hypothesis incorporates the *time* component by describing the generation of classes of the immune response ¹⁵. Here, I would like to explain the basic concepts of the workings of the immune system. These include analytic-homeostatic integrity principle, which highlights the micro-environmental influence (during antigen challenge) and incorporates the *time* dimension. This is an elaboration of the *Integrity* model ¹⁶⁻²⁰.

Preservation of integrity vs. integration

The preservation of integrity principle includes biologic heritable components that enable living cells to keep certain shape and size. Cells' integrity preservation diversified and evolved to a complex state in animals and plants, and it includes dynamic and organized set of functions controlled by various genomes and interactions with environment.

A remarkable feature of eukaryotic cell is its mitochondrion, which originated from symbiosis of two bacterial cells. It increased cellular complexity and opened a possibility to build multicellular life forms beyond colonies or biofilms. This was due to an advantage of having increased energy potential either from division of labor or by having multiple sources of energy. Interestingly, symbiosis (that made the eukaryotic cell) did not provide a selective advantage for the survival (of the fittest cell) as bacteria still persist in nature. Therefore, a ubiquitous force that advances complexity of organized life and promotes commensalism we should call the integration drive (as an add-on to the integrity preservation, which resets it at a higher complexity level). This is different from a drive that generates diversity of life forms. However, both forces work in parallel creating and diversifying beings that are under constant natural selection pressure.

Many would suggest that the above-mentioned symbiotic event happened by chance and not by necessity. Was this chance evolutionarily upgraded such that living organisms could actively seek companions for potential commensalism or symbiosis? Perhaps this quest would only reflect an increased likelihood for accomplishing commensalism. Even so, I would argue that the immune system includes such an activity in addition to its defense function, and furthermore, if beneficent associations were found, it would protect them from its own bio-destructive effectors. Here is how: let us start first by defining basic relationship between the immune system and the integrity principle, and then compare the latter with self-nonsel discrimination principle. Then, I shall describe a possible evolution of integrative function of the immune system and present its basic concepts. However, an in-depth analysis of the workings of the immune system in connection to various experimental observations and pathologies will be described elsewhere as it would cross the scope of this article.

Throughout evolution, preservation of integrity had the highest priority for survival of an organism until its reproductive age. As a defensive department, the immune system has the unique ability to infiltrate almost all other organs and is likely to assume a guardian-of-integrity role within the boundaries of an organism. There are two boundaries to be distinguished: conceptual and real. The first is the complexity formed by the interaction of highly organized, high-energy state of 'self', and the second is chaos, outside the protective integrity. The real border is the skin, epithelia of digestive, respiratory, urogenital tissues and the eyes. Both boundaries contain genetic and epigenetic elements. Like the defensive apparatus of a fictitious state, the immune system neither loses time on trying to guess how the potential and unknown enemies (nonself) might look like, nor builds a range of potential weapons against them. Instead, it uses already available integrative communications (adhesion, cytokines) and tools (i.e. oxidative radicals, pore making molecules, proteases and apoptotic signals) for defense and for

maintaining the organism's, tissue's or cell's integrity. Aging decreases the level of integrity, and eventually it becomes unbearable for any protection mechanism to preserve an individual.

The self-nonsel self discrimination vs. integrity preservation principle

The S/NS has been proposed to be the driving force for the evolution of the immune system. The differences between self and nonself molecules are indistinguishable at the molecular level. Thus a biological control for selecting of what is self or nonself seems to be required. Because this cannot be based on a decision made from outside of the system, the system has to learn what is self. If self does not change during life, this principle might work. However, self changes during life (idiotypes, bacterial flora ²¹, and at the onset of puberty) and this "decision maker" becomes elusive. The self/nonself discrimination is not a ubiquitous principle in life, as we neither find it in plants (they neither reject allografts nor xenografts), nor in invertebrates where an analog of transplant rejection involves species rather than individual incompatibility.

In contrast, preservation of integrity trespasses living kingdoms as a principle and as a force that maintains life. It started when the first cell was formed during evolution. The preservation of integrity can be described in philosophical terms as reaction that has been selected to counter random destructive action. This reaction operates under the homeostatic principle in higher organisms. For example, let us suppose that integrity of a living cell/organism represents a particular level of a normal state of cellular and subcellular interactions including metabolism. The constant challenge to disintegrate the complexity of cell, tissue, organ or organism during the life of an individual is *an action* that (if not completely destructed) would set in motion positive or negative feedbacks. Restorative reactive process(es) can be called *negative feedback*. Distress (with delayed apoptotic death) would represent positive feedback. If a tissue starts proliferating uncontrollably, like in tumors, it would be another type of the positive feedback. Benign tumors would undergo a short spell of positive feedback and

eventually stop growing, albeit at the different level of integrity. This stop is theoretically similar to the renewal of integrity after tissue damage. Processes that precede the restoration of integrity can be perceived as to follow the *analytic* principle. This term will be useful in explaining the difference in reactions towards potential symbionts and real pathogens. Also, it would explain the development of immunologic tolerance with short- and long-term memory. The difference in explaining immunologic phenomena between *integrity* and S/NS principles is in the *time* dimension. The description of the *integrity* principle states that each reaction is a timely response to a preceding action (thus, the *integrity* principle includes the *time* component), whereas the concept of discrimination between self and nonself is *timeless*, as it is a choice of the system at a particular time point. For this reason S/NS theory requires more complex explanation to depict the workings of the immune system in order to incorporate the *time* dimension. Later, we would see that the S-NS discrimination principle could depict a simple model of events observed in approximately one-third of theoretical predictions of the integrity hypothesis.

The integrity model and how the immune system could have evolved

In describing the workings of the immune system we can start with definition that the protection and allowance for the restoration of damaged integrity is the main function of immunity. However, the role of immunity is widely regarded as protection against pathogenic intruders including viruses, bacteria, and unicellular and metazoan parasites. There is no disagreement with such a notion as microorganisms are the most common disintegrators of higher living organisms.

How would the immune system evolve according to the integrity-repair principle? Let us first simplify matters and use imagined immune systems, thought of as "thingies", as a conceptual model.

Protection against pathogen. For a start, there are two thingies: Host thingy (Host Tg) and lethal thingy (Lethal Tg; which represents a pathogen) are equal except for the ability of

Lethal Tg to infect and to kill Host Tg (Fig.1A). Host Tg would survive if a mutant could be selected rendering Host Tg a bio-destructive weapon (BioDeath) that can kill the intruder. A potential BioDeath Tg mutant and Host Tg would be the same except for the BioDeath mutation. BioDeath Tg could not have arisen with just this BioDeath mutation, because the use of BioDeath weapon would have killed BioDeath-Tg itself, leaving no progeny. It is, therefore, necessary for Host Tg to protect itself from the BioDeath weapon. This is established by an integrity-protection (IntPro) mutation. Because IntPro function must appear before the bio-destructive function, only the Host Tg --> IntPro-Tg --> IntPro-BioDeath-Tg evolutionary pathway can exist (Fig.1B).

The IntPro mutation might have arisen in one of the genes encoding molecules required for building normal cellular components. A good candidate would be a chaperone that is used to ascertain proper conformation of structural building blocks. Such a molecule with a mutation IntPro, would be adapted to avert host destruction by its own bio-destructive component (Fig.1B).

According to integrity preservation principle, IntPro-BioDeath-Tg defends itself and kills Lethal Tg by evading its own annihilation with IntPro mechanism while applying the effective BioDeath destruction of Lethal Tg. The IntPro function could be inducible or constitutive. If inducible, IntPro should be expressed simultaneously with BioDeath, or it should precede the expression of BioDeath. It would also require an unspecific signal that would be a sign of a broken integrity or penetration of an intruder. The IntPro would function in the localization and identification of the site of intrusion, demarcation of an intruder by soluble mediators, and attraction of components of the BioDeath weapon. IntPro can sufficiently protect the host if the intruder is well sequestered in space. Primordial BioDeath effectors would be attracted to these sites and would destruct the pathogen (Lethal Tg). Such effectors might include a natural killer (NK)-cell like mechanism, because Lethal Tg is deficient in host IntPro and (or) BioDeath

markers. The lack of positive identification of self would be, thus, the only prerequisite for the elimination of Lethal Tg. There would be no need to discriminate a nonself antigen (Lethal).

Symbionts. Let us now consider a situation in which a potential symbiont (Sym Tg) would be present alongside with IntPro-BioDeath-Tg and Lethal Tg (Fig. 2). Both Lethal Tg and Sym Tg can intrude into the IntPro-BioDeath-Tg. In both cases the penetration event would be similar. Separation of IntPro and BioDeath functions in *space* can bestow IntPro-BioDeath-Tg an opportunity to treat symbionts differently from pathogens provided some kind of *time*-dependent analysis mechanism for intrusion would evolve. A disruption-analysis (DisAn) carrying thingy (IntPro-DisAn-BioDeath-Tg) would have a choice to select potential symbionts and to establish tolerance in a direct way, without having the need, first, to discriminate between self and nonself, and then to establish tolerance to nonself. Intrusion by Lethal Tg or Sym Tg could upregulate the DisAn function, and hold the triggering of the bio-destructive weapon for some time. If the intruder negatively interferes with the functioning of the host, the result would be the elimination of Lethal Tg (Fig. 2A). However, if the functional disturbance were not detected, the initiated response would cease and integration would ensue (Fig. 2B). Thus, *analysis* requires a time lag for assessing the risks of potential symbiosis, or, in other words, there is dissociation in *space* and *time* between the initiating and effector arms of the protection mechanism. This would lead to the development of receptor specificities within the system in evolutionary sense. The generated repertoire would ascertain proper identification and communication of protection mechanism factors between *analysis* and *renewal*.

The immune repertoire. The predecessors of NK-like cells would recognize the lack of IntPro, DisAn or BioDeath markers with IntPro- or DisAn- or BioDeath-specific receptors. It is likely that these receptors would not initially be clonally distributed. The immune repertoire of receptor specificities might have arisen on the basis of somatic rearrangements and/or mutations of receptor genes for IntPro. NK-like cells with diverged receptors could have recognized self-

structures in combination with antigens from the intruder. This self-structure was likely IntPro, because it had the ability to chop other molecules, and because further along the evolutionary pathway, the IntPro gene-pool would have become enlarged by incorporating protection against biochemical influences of the environment. The latter assured that at least some IntPro functions would be constitutively expressed. To activate such NK-like cell, one of the receptors should have provided the activating signal. The evolutionary line could have branched here. The diversified receptor might have remained inhibitory on some cells or become activating on the others. The activating-diversified receptor would have to be put under the control of an inhibitory one. It would, otherwise, pose a threat as a potential autotoxic weapon. Such cells would be activated through the diversified receptor, provided the target lacked self IntPro or DisAn markers, and triggering of BioDeath function would ensue. DisAn could have evolved through a duplication of the IntPro gene, which is, perhaps, inducible by penetration. If DisAn would be inducible, DisAn-specific inhibitory receptors on NK-cell predecessors should be selected against in the course of evolution. So, our NK-like cell would end up having just one constitutively expressed receptor--the diversified and inhibitory one. These predecessors of T cells would use the other -- non-diversified receptor to obtain a (second) signal for activation. Thus, a likely candidate for predecessor of costimulation would be the DisAn function.

I hypothesize that diversification of antigen receptors was driven by the need of having an operational symbiont/pathogen *analysis* mechanism. This mechanism also implies the formation of short-term memory (effector) cells against intruders.

The "analysis" mechanism. The structural/mechanical loss of integrity (i.e. adhesion break-up) between cells in a tissue, or a cellular disruption (including loss of adhesive contacts between neighboring cells) could start a non-specific response, a part of the integrity-disruption signal. The decrease of tissue integrity signals and their complexity would be sensed by a specialized factor (i.e. dendritic cell) and would lead to activation of a *disruption-analysis*

function. This includes phagocytosis of antigens in the neighborhood, migration to specialized compartments and expression of processed proteins as peptides in the context of IntPro. If negative functional disturbance would be detected, the DisAn function would start the cross-talk with a cell that is a T-cell equivalent. Thus, the signal for disruption of integrity would upregulate the signal that allows integrity-repair. The activation of the effectors (macrophage, cytotoxic cell and B-plasma cell equivalents) would ultimately lead to destruction of an intruder. If there would be no calamity in the functional sense, tolerance of the state (and possibly of its perpetrator) that induced disruption would ensue. The effectors would be silenced (suppressed). But if the potential symbiont would turn out to be a pathogen, then the functional disturbance would give a signal for its elimination. The effector cell that could attack the pathogen is the same that was activated and silenced previously, and would thus need to go through a short-term anergic state before becoming reactivated.

This description can be compared with the innate and specific immune system. We can take MHC Class I and Class II molecules, together with proteasomes, peptide loaders and other molecules involved in antigen presentation, as possible descendants of IntPro. Costimulation and cross-talk could be descendants of DisAn function. The corresponding receptors for IntPro-like molecules might have given rise to killing inhibitory receptors (KIRs) and killing activating receptors (KARs) on NK cells, or to T-cell receptors (TCRs). The primordial IntPro-like receptors might have been recruited from the pool of soluble molecules involved in demarcation of Lethal Tg in the IntPro-BioDeath Tg. From the same pool of soluble mediators, the contemporary antibodies and B-cell receptors (BCRs) could also maintain descent.

The basic operating rules of the immune system

The integrity-repair mechanism described above can function as the immune system if IntPro is substituted with antigen presentation and recognition, and DisAn with costimulation or help. For simplicity, the IntPro and DisAn functions can be represented by signal[1] and

signal[2], respectively. A disruption of integrity would be represented by signal[3]. The normal integrity signals are multiple, and their disruption can have a variety of modulatory effects on dendritic cells, APCs and lymphocytes. These can be grouped into two extremes, so that their modulatory capabilities are understood as logical attributes of each signal, having either true or false qualities. Thus, a set of true signals would result in actions such as the immune response in the form of rejecting the pathogen. The Boolean parameter is used as means to help in understanding different outcomes of the immune response. It might represent physiologically different circumstances within each cell of the immune system regarding variability in the engagement of signaling pathways, differentiation stage and epigenetic state of responding genes.

The modes of action. The integrity model proposes a set of rules for all specific lymphocytes. There are four populations to be distinguished: a) developing lymphocytes, b) naive peripheral, c) effector (short-term memory), and d) long-term memory cells. They are commanded by the three signals: signal[1], [2] and [3]. In addition, a Boolean parameter assigns the true or false quality of each particular signal.

Signal[1] can represent TCR--peptide/MHC, or BCR--antigen interaction. Its true/false quality, for T cells for example, might be determined at the level of T cell recognizing displayed peptide/MHC complexes. The false signal[1] for T cells would resemble a situation when a peptide has a specific conformation so that the TCR cannot be engaged for a sufficient amount of time to generate fully operational signal[1] (a kind of prematurely abolished signal[1]). These peptides are known as partial agonists.

The true signal[2] delivers, for example, costimulation to T cells via CD28--CD80/86 (B7.1/7.2) binding, or T-cell help to B cells or precursors of cytotoxic T cells (pCTL) (Fig. 3 and Fig. 4). The false signal[2], for T cells for example, would include interaction with CTLA4 (CD152)

during the activation. The change would block delivery of signal[1] to falsely-primed effector T cell, upon repeated interaction with the target APC (Fig. 4).

Signal[3] with its logical attributes tunes the immune system to operate under two different modes:

1. The basic mode. This mode of action describes the activity of the system in the absence of signal[3]. The integrity signals are abundant and in communicational order. The cells that can monitor integrity signals perceive them and operate under basic conditions. In this mode, signal[1] tolerizes naive and memory T or B cells by providing the death signal, but activates them in combination with (aberrantly) provided signal[2], leading to immunopathology.

2. The *analysis/renewal* mode. Here, the activity of the immune system is under the influence of signal[3]. There are at least two inducing components depending on what type of integrity was broken: structural and functional: 1) a local break of structural integrity in tissue organization (including adhesion, break-up of integrin--matrix interactions) that can mobilize dendritic cells (+Sd in Fig.3 and Fig. 4) a soluble or cellular (functional) component that can attract non-specific and specific cells, signal alert and modulate other signals (+Fd in Fig. 3 and Fig. 4). This mode of operation lasts until the signaling stops, which, by definition, ends the immune response.

a.) True signal[3]: True signal[3], in principle, upregulates the availability of cells to encounter and receive true signal[2] which is, for T cells, normally provided by the dendritic cells or other types of APCs. In combination with true signal[1] it initiates the immune response, i.e. it generates the first Th effector cells. It allows, then, effector Th to deliver help to B and CD8 (pCTL) cells. There is variability in the kind of functional damage (+Fd in Fig. 3) depending on tissues where damage happened that controls and selects the class of the response. This could also involve recruitment and activation of various types of earliest innate immune cells, and transmission of such +Fd to APCs resulting with APCs' maturation or functional capacitation (to

modulate the response). Furthermore, naive B (nB) cell and pCTL, beside true signal[1], also require a true signal[3] to mature into effectors themselves. For effectors like the *activated B cell* and the 'CTL', a true signal[1] suffices *to become Ig-switched - hypermutated secreting cell* or 'to kill', respectively (Fig. 3 and Fig. 4).

b). False signal[3]: This is an incomplete or full imitation of unperturbed integrity, or an incomplete mimic of disrupted integrity. False signal[3] would induce false signal[2] and may modulate the signal[1]. The consequences of delivery of the combination of true signal[1] and false signal[2] to naïve Th (nTh) cells might vary from premature shut-off (suppression), anergy to clonal deletion, (Fig. 4) with the latter, perhaps, occurring after a different period of time when compared to only-signal[1]-induced deletion. Perhaps this is the strategy that some tumors and parasites use to evade the immune attack. The false signal[1] would cause ignorance, partial activation or suppression (and natural Tregs), seen as secretion of some cytokines without the significant proliferative response. The false signal[3] in which there is no structural damage (-Sd), but only functional change of the modulatory kind (-F modulatory in Fig. 4) would give rise to iTregs, which can, for example, protect actively commensals or help in abrogating autoimmunity.

Development of specific immunocytes. During development, thymus and bone marrow provide the context that delivers false signal[3], simulating the disruption of integrity. The organism can use this function to select the repertoire of developing T cells (and perhaps B cells in the bone marrow). The cells carrying receptors for self-antigens are selected only if they have somatically rearranged their receptors not to recognize self specificities. The rearrangement that provides false signal[1] would be selected for further development. All other cells would die. This is based on the displayed set of cell-surface proteins or peptide-MHC complexes, for developing B cells or thymocytes, respectively. A different form of the false signal[1] (i.e., pre-BCR,-TCR/ligand) would be employed to check the structures and intracellular mediators

required later for the true signal. Another checkpoint in the development would assess the function of the signal[2]. Thus, a combination of false signal[1] (involving BCR/?, and TCR/partial agonist) and false signal[2] (different from the above mentioned example) may be seen as positive selection of thymocytes, and, possibly, B cells (Table 1).

The basic immune response. The switch between the modes of operation initiates or stops the immune response. The disruption of structural and functional integrity of a tissue starts *analysis* of the functional interference of an intruder with the host, and, if “true”, initiates competition of cells for the activation. Differences in the micro-environmental factors due to a variety of broken integrity signals, lead to a change from true to false signal[3] (or vice versa) in *space* and *time*. Such a process would result in increased competition for epitopes on APCs between lymphocyte populations that were set in motion (by signals [1+2]), that were dying (by signal[1]-only) or that were pacified (by false signal[2]). The true functional disruption of integrity thus leads to bio-destruction of a pathogen at sites of intrusion via humoral and/or cellular immune response. The false functional disruption, or the lack of it, leads to peripheral tolerance such as we observe in commensalism. The mechanism can also explain the generation of regulatory T cells as a result of the immune attack against such commensals. It means that the immune system would (ideally) have two functions: it could give asylum and protect useful microorganisms, whereas it would destroy pathogens upon intrusion.

Conclusion

The immune system senses disruption of integrity of tissues and cells (other than apoptosis or normal programmed cell death) through specialized cells, and uses cells and molecules as effector tools and messengers in an attempt to restore the previous state of organization. There are three signals that command the workings of the immune system. Each of them can be modulated by non-specific, cytokine, chemokine, and cell-cell or cell-matrix network of signals. The modulatory effects can be grouped into two polarized extremes that can

be logically comprehended as of true or false quality, which are, thus, assigned to each particular signal.

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Figure legends

Fig. 1. The thingie experiment: The evolution from primordial integrity-repair mechanism. **A.** The consequences of the interaction between host and lethal thingie. **B.** The consequences of the interaction between evolved host thingie into *integrity-protection bio-destructive* thingie with lethal thingie.

Fig. 2. The evolution of disruption analysis component. **A.** The interaction between additionally evolved host thingie (*integrity-protection disruption-analysis bio-destructive* thingie) and pathogen (lethal thingie). **B.** The interaction between additionally evolved host thingie and potential symbiont (sym thingie).

Fig. 3. The causes and effects of true signal[3].

Fig. 4. The causes and consequences of false signal[3].

Fig. 1 A.

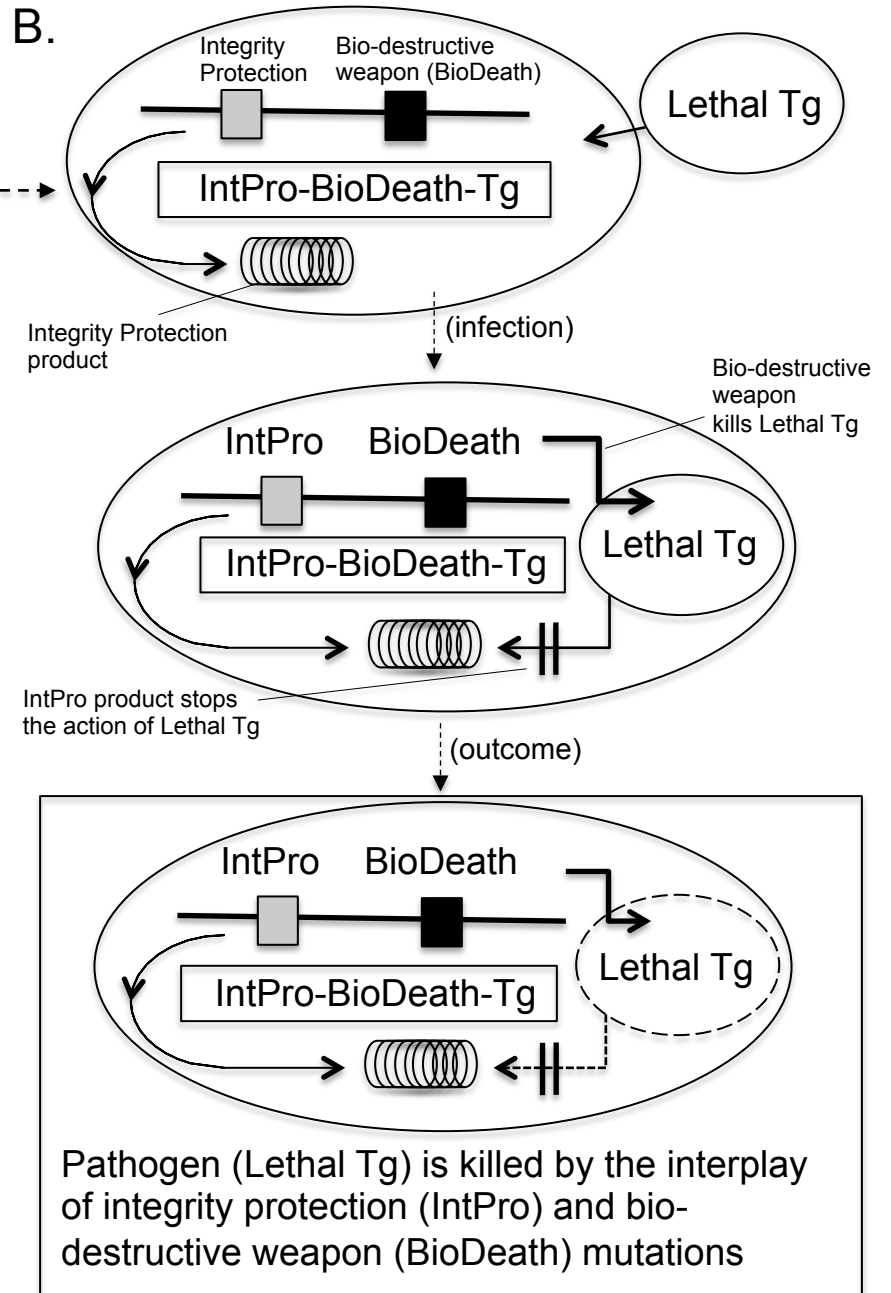
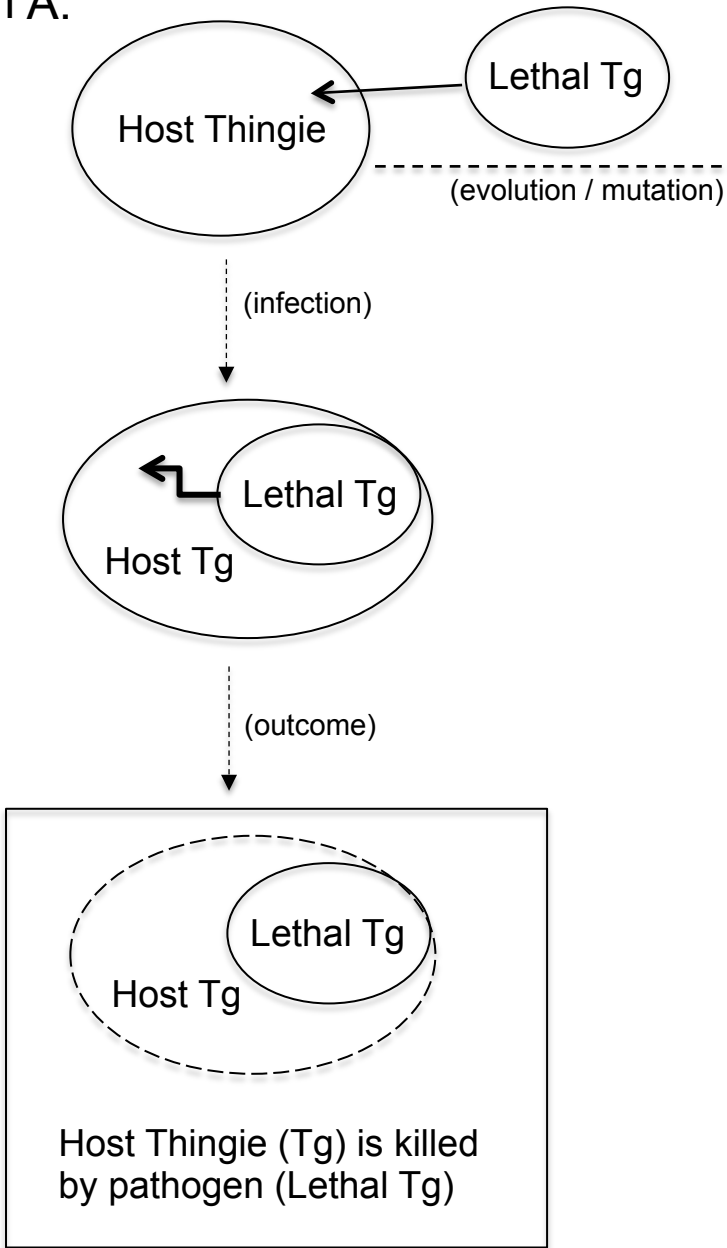
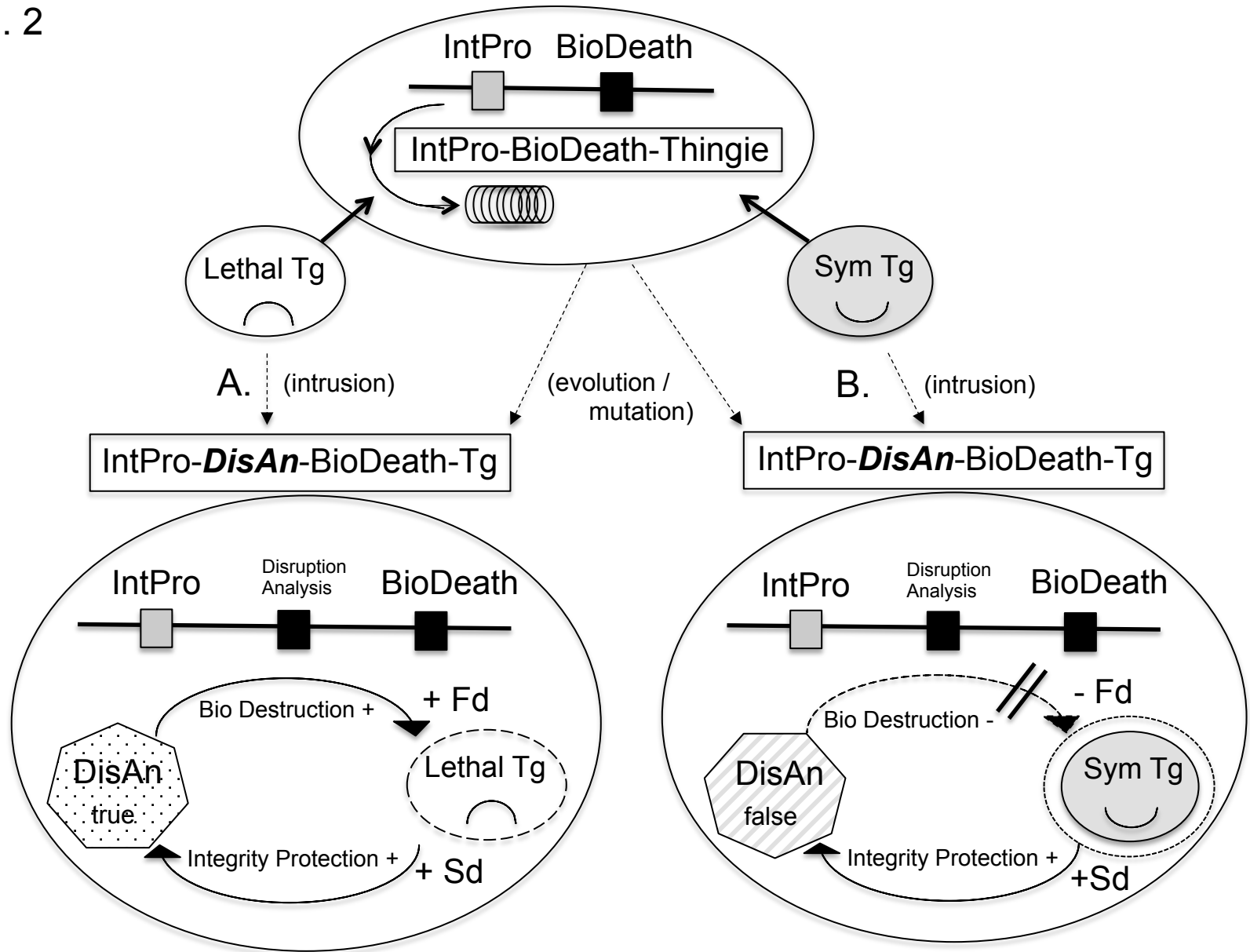


Fig. 2



Disruption analysis (DisAn) mutation detects structural (Sd) and functional (Fd) damages. Outcome: rejection of infection

Disruption analysis (DisAn) mutation detects structural (Sd) without functional (Fd) damage. Outcome: integration

Fig. 3

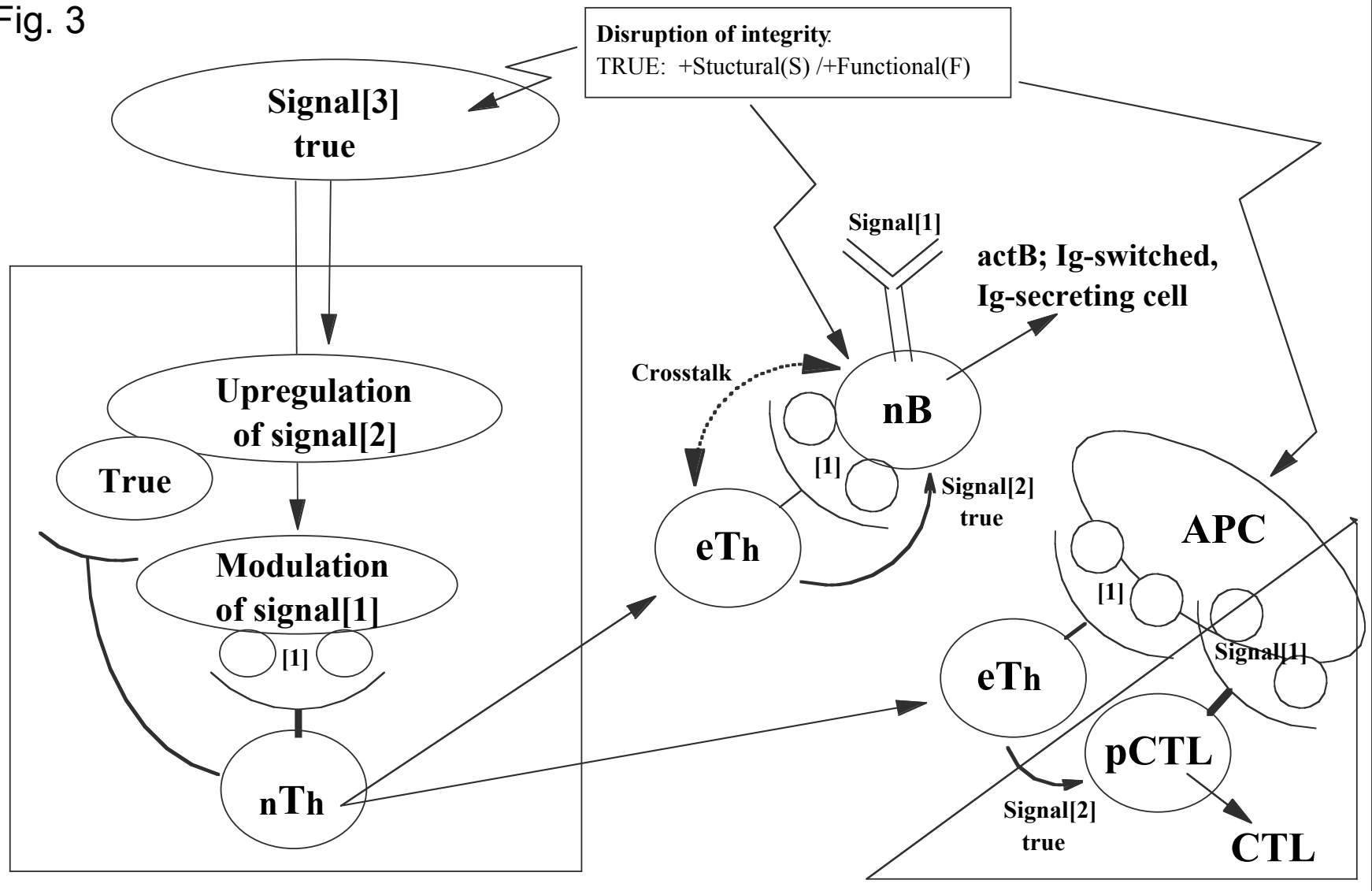


Fig. 4

